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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

ART UNIT	PAPER NUMBER
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DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/611,992

Applicant(s)

WU ET AL.

Examiner

Ruth A Davis

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1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-28 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-28 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claims ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s): ____
- 18) ☐ Interview Summary (PTO-413) Paper No(s) ____
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1 - 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 - 28 are drawn to a method for cultivation of filamentous fungi, however are indefinite for reciting "inoculating an inoculum" because the origin of the inoculum is not defined. It is unclear how "an inoculum" could cultivate filamentous fungus, or metabolites thereof. The claims as written, do not adequately define what applicant regards as the invention. For example, in claim 1 applicant may more clearly describe the invention by replacing "inoculating an inoculum" with "inoculating said medium with said filamentous fungi."

Claims 7-9, 15-18, 23-26 are drawn to a method for cultivation of filamentous fungi, however are indefinite for reciting "a step of inoculating said fungi after step (a)" because it is unclear whether the fungi is being inoculated or if the fungi itself is the inoculating agent. It is confusing where and from what the inoculum is being obtained. They are further confusing by reciting "to obtain said inoculum" because the origin of the inoculum is not defined. The claims, as written, do not adequately define what applicant regards as the invention.

Claims 8-10, 16-18, 24-26 are indefinite for reciting "inoculating a culture cultivated" because it does not specifically identify what culture is being cultivated thereby failing to distinctly identify what applicant regards as the invention. Applicant could more clearly claim

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the invention by replacing "a culture" with "said culture" or specifically naming the culture, e.g. in claim 8, "inoculating said filamentous fungi culture".

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(c) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claims 1-4, 6-13, 15-21, 23-28 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Wu et al (May 2000).

Applicant claims a method for cultivation of filamentous fungi, specifically *Monascus* species and metabolites thereof, whereby the filamentous fungi is inoculated and incubated on an agar media, the spores are washed with sterile water, cultivated in a medium containing a nutritionally solid substrate, specifically grain, via shaking, and is placed in an airlift bioreactor with a net draft tube for fermentation. The resulting fungal culture is inoculated into a prepared medium containing grain as a nutritionally solid substrate, nitrogen, inorganic salts, and trace elements, then placed in a bioreactor for fermentation using the fed batch process wherein the batch contains nitrogen and a grain substrate.

Wu et al teaches a cultivation of a *Monascus* species for the production of metabolites whereby the an inoculum of *Monascus* was prepared from a stock culture grown on a agar plate, suspended in a nutrient broth and incubated via shaking, then cultivated in a medium containing rice particles and was placed in bubble column equipped with wire mesh draft tubes to carry out batch culture fermentation (Materials and methods, Cultivation of *M.purpureus* pg. 543). The nutrient broth contained rice particles as the nutritionally solid substrate, a nitrogen source, trace salts and elements (Microorganisms and media, pg. 543).

The reference anticipates the subject matter of the claimed invention.

5. Claims 1-4, 13 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamaguchi et al (US 3,765,906).

Applicant claims a method for cultivation of filamentous fungi and metabolites thereof, whereby said fungi may be *Monascus*, *Penicillium*, or *Aspergillus*, comprising the steps of: preparing a medium with a nutritionally solid substrate, specifically grain, inoculating the fungi into the medium and placing it in a bioreactor for fermentation.

Yamaguchi et al teaches a method for cultivating a *Monascus* species and non-soluble pigments thereof, whereby a culture medium containing rice powder is inoculated with a *Monascus* species and is placed in a jar fermentor for fermentation (col.3 example 1).

The reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 6, 11-12, 19-20, and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi et al (3,765,906) in view of Johal et al (4,954,440) and Eyal et al (5,077,201).

Applicant claims a method for cultivation of filamentous fungi and metabolites thereof, whereby said fungi may be *Monascus*, *Penicillium*, or *Aspergillus*, comprising the steps of preparing a medium with a nutritionally solid substrate, nitrogen source, inorganic salts and trace elements, inoculating said fungi into the medium and placing it in a bioreactor for fermentation using the fed batch process, wherein the batch medium comprises a nitrogen source and nutritionally solid substrate.

Yamaguchi et al teaches a method for cultivating a *Monascus* species and metabolites thereof, wherein a culture medium containing rice powder is inoculated with a *Monascus* species and is placed in a jar fermentor for fermentation (col.3 example 1).

The reference does not teach a medium additionally comprising a nitrogen source, inorganic salts and trace elements or cultivating the fungi with the fed batch process wherein the batch medium contains a nitrogen source and a nutritionally solid substrate. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include a nitrogen source, inorganic salts and trace elements in the culture medium of

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Yamaguchi because Johal et al teaches a nutrient medium for the cultivation of filamentous fungi normally contains nitrogen sources, inorganic nutrients such as trace salts and trace elements (col. 4 lines 29-24, lines 48-53). In addition, Johal et al teaches typical cultivation methods employed for filamentous fungi in include batch fermentation and the fed batch process (col.3 lines 25-30). One would have been motivated by Johal et al at the time the invention was made to include the additional nutrients, as they are part of the minimal medium requirements to sustain growth and production of successful filamentous fungi.

One of ordinary skill in the art would have been further motivated to utilize the fed batch process in the method of Yamaguchi et al because Eyal et al discloses that the fed batch process is advantageous to maximize production of fungal metabolites (col. 4 lines 15-18). Furthermore, the inclusion of a nitrogen source and nutritionally solid substrate to the batch medium would have been obvious to one of ordinary skill in the art because with additional media supplied via fed batch, the fungi would need an adequate replenishment of nutrients as it utilized its original source.

8. Claims 5, 7-8, 14-16, 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi et al (US 3,765,906) in view of Yueh et al (PN 4,418,080) and Haas et al (PN 4,031,250).

Applicant claims a method for cultivation of filamentous fungi and metabolites thereof, specifically *Monascus*, whereby a medium is prepared comprising a nutritionally solid substrate, specifically grain, and is inoculated with an inoculum of said fungi then placed in a bioreactor for fermentation. The grain is previously husked, cocked, and sterilized. The inoculum is

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obtained from a stock fungi that is cultured on an agar plate, incubated, washed, and cultivated in a medium containing said substrate via shaking.

Yamaguchi et al teaches a method for cultivating a *Monascus* species and metabolites thereof, wherein a culture medium containing rice powder is inoculated with a *Monascus* species and is placed in a jar fermentor for fermentation (col.3 example 1). The reference does not teach using a stock culture as the source of said fungal inoculum whereby the stock culture is grown on an agar plate, washed, cultivated in suspension with a grain substrate in an incubator while shaking, and placed in a bioreactor for fermentation.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to obtain the fungal inoculum from a stock culture as claimed by applicant because Yueh et al teaches the cultivation of *Monascus* in a medium containing a solid grain substrate (abstract; col.1 lines 38-40, 43-45; col.2 lines 38-42) whereby an inoculum of *Monascus* is prepared from a previously grown liquid culture which is incubated while shaking (example II). The grain is pre-sterilized by moist heat or autoclave (col.2 lines 19-22). The previously grown culture is disclosed as obtainable by any known method in the art (col.2 lines 13-16). The obtained inoculum is further inoculated into the nutritionally solid substrate medium and allowed to ferment (col.2 lines 27-31).

Yueh et al does not disclose the specific use of an agar plate to grow the stock culture, however, Haas et al teaches the cultivation of *Monascus* on a grain substrate whereby the culture is obtained from a stock culture grown on an agar slant or potato dextrose agar (col.1 lines 56-63). The reference further teaches that a fungal suspension in liquid medium is typically formed prior to being inoculated into a grain substrate (col.2 lines 5-8). For example, the slant or agar

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plate on which the fungus was grown is washed with water to ensure a turbid suspension (col.2 lines 8-12). The suspension is then inoculated into a grain-containing medium (col.2 lines 12-13) where in the grain is heated/autoclaved for sterilization (col.1 lines 65-68). The resulting culture is further utilized to inoculate media for fermentation (col.2 lines 15-16).

One of ordinary skill in the art would have been motivated at the time the invention was made to prepare an inoculum as disclosed by the above references for use in the method of Yamaguchi et al because they are commonplace and typical procedures that are practiced by those skilled in the art. Further, it would have been obvious to one of ordinary skill to husk and cock the grain prior to sterilization because they are conventional steps in preparing grain to necessitate its use.

9. Claims 9-10, 17-18, 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi et al (US 3,765,906) in view of Yuch et al (PN 4,418,080) and Haas et al (PN 4,031,250), and in further view of Tung et al.

Applicant claims a method for cultivation of filamentous fungi and metabolites thereof, specifically *Monascus*, whereby a medium is prepared comprising a nutritionally solid substrate, specifically grain, and inoculated with an inoculum of said fungi then placed in a pneumatic airlift bioreactor with a net draft tube for fermentation. Prior to addition to the medium, the grain is husked, cocked, and sterilized. The inoculum is obtained from a stock fungi that is cultured on an agar plate, incubated, washed, and cultivated in a medium containing said substrate via shaking.

Yamaguchi et al teaches a method for cultivating a *Monascus* species and metabolites thereof, wherein a culture medium containing rice powder is inoculated with a *Monascus* species

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and is placed in a jar fermentor for fermentation (col.3 example 1). The reference does not teach using a stock culture as the source of said fungal inoculum whereby the stock culture is grown on an agar plate, washed, cultivated in suspension with a grain substrate in an incubator while shaking, and placed in a bioreactor for fermentation.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to obtain the fungal inoculum from a stock culture as claimed by applicant because Yueh et al teaches the cultivation of *Monascus* in a medium containing a solid grain substrate (abstract: col.1 lines 38-40, 43-45; col.2 lines 38-42) whereby an inoculum of *Monascus* is prepared from a previously grown liquid culture which is incubated while shaking (example II). The grain is pre-sterilized by moist heat or autoclave (col.2 lines 19-22). The previously grown culture is disclosed as obtainable by any known method in the art (col.2 lines 13-16). The obtained inoculum is further inoculated into the nutritionally solid substrate medium and allowed to ferment (col.2 lines 27-31).

Yueh et al does not disclose the specific use of an agar plate to grow the stock culture, however, Haas et al teaches the cultivation of *Monascus* on a grain substrate whereby the culture is obtained from a stock culture grown on an agar slant or potato dextrose agar (col.1 lines 56-63). The reference further teaches that a fungal suspension in liquid medium is typically formed prior to being inoculated into a grain substrate (col.2 lines 5-8). For example, the slant or agar plate on which the fungus was grown is washed with water to ensure a turbid suspension (col.2 lines 8-12). The suspension is then inoculated into a grain-containing medium (col.2 lines 12-13) where in the grain is heated autoclaved for sterilization (col.1 lines 65-68). The resulting culture is further utilized to inoculate media for fermentation (col.2 lines 15-16).

One of ordinary skill in the art would have been motivated at the time the invention was made to prepare an inoculum as disclosed by the above references for use in the method of Yamaguchi et al because they are commonplace and typical procedures that are practiced by those skilled in the art. Further, it would have been obvious to one of ordinary skill to husk and cock the grain prior to sterilization because they are conventional steps in preparing grain to necessitate its use.

The above references do not teach the use of a pneumatic airlift bioreactor with a net draft tube, however it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize this type of bioreactor because Tung et al teaches an airlift reactor with double net draft tubes is advantageous for fermentation in that cultivation time is significantly shortened (abstract). Tung et al further teaches single net draft tubes perform better than a bubble column (introduction). One of ordinary skill in the art would have been motivated to utilize the single or double net draft tube over a bubble column in the methods of the references cited above to improve the efficacy of the fermentation process and to increase production and scale up efficiency.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruth A Davis whose telephone number is 703-308-6310. The examiner can normally be reached on M-H (7:00-4:30); altn. F (7:00-3:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

November 27, 2000

A handwritten signature in black ink, appearing to read 'L. B. Lankford, Jr.', with a stylized, cursive script.

LEON B. LANKFORD, JR.
PRIMARY EXAMINER